UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,293	09/23/2004	Liangzhi Xie	21038P	3707

210 7590 01/18/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,293	XIE ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1648.** Claims 1-15 are pending and under examination.

Claims Summary

The claims are drawn to a method of producing a virus, such as adenovirus, comprising the following steps:

a) Inoculate and culture host cells in an appropriate medium at a temperature below a physiological optimum for host cell growth;

b) Infect the host cells with a virus;

c) Culture the virus-infected host cells at or near a physiologically optimum temperature for producing virus;

d) Harvest the virus and/or cells containing virus from the culture; and,

e) Purify virus away from host cell and culture contaminants.

In another embodiment, the temperature of the host cell culture of step a) is initially at or near a temperature near a physiological optimum for host cell growth, then shifted to a temperature below a physiological optimum for host cell growth prior to infecting the host cells with a virus. The culture temperature is lowered to a sub-optimal level for at least about 24 hours prior to infecting the host cells with the virus. In another embodiment, the culture temperature is lowered to a sub-optimal level for up to the entire cell passages prior to infecting the host cells with the virus. Specifically, the temperature for cell growth at the initial

temperature is between 35°C and 38°C. The temperature is then shifted to a temperature between 31°C and 34°C. The temperature for growth of infected cells is between about 36°C to 38°C.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. There are three aspects of this rejection:

1) The metes and bounds of claims 1-8, with respect to the phrases, "at a temperature below a physiological optimum for host cell growth", and, "at or near a physiologically optimum temperature for producing virus", cannot be determined. The specification offers various teachings regarding the meaning of optimal temperatures.

At page 2, lines 26-30:

"The physiological temperature of 37°C has been shown to be optimal for growth of a majority of mammalian cell lines. Temperatures below 37°C historically are shown to reduce cell growth rate, overall cell metabolism, and specific product formation in mammalian cells"...

At page 2, lines 31-33:

"The optimal temperature for virus production depends on the virus strain and the host cell line, but has most often been found to be below 37°C"...

At page 3, lines 3-4:

"Temperatures above 37°C are generally not suitable or even non-permissive for virus replication"...

At page 7, lines 11- discloses the following:

"It is an accepted practice that cell growth in culture is typically conducted at the physiological temperature of 37°C and virus propagation is conducted either at the same temperature as cell growth or shifted downward to a lower temperature. The basis for such a production strategy has been that culture at the physiological temperature allows optimal cell growth but the optimal temperature for the production of many viruses is usually lower due to improved productivity and stability."

Given this guidance, it remains unclear what temperatures are encompassed by the phrases, "at a temperature below a physiological optimum for host cell growth", and, "at or near a physiologically optimum temperature for producing virus". While the physiological optimum may be generally 37°C, it is unclear what temperatures are encompassed when the temperatures are "below" 37°C, for example. Similarly, it is unclear what temperatures are encompassed when the temperatures are "near" 37°C, for example. Therefore, even if the optimal temperature is known to be 37°C, the temperatures below and near 37°C are not so clearly defined such that one of skill in the art would be able to determine what temperatures are encompassed by the claims.

2) Claims 9-15 recite temperature ranges that are not clear; particularly, "from between 31°C and 34°C". The use of the word "from" indicates that a range is to be set forth. It is not clear whether the phrase means that the temperature is between 31°C and 34°C, or if the phrase means that starting point of the temperature range is between 31°C and 34°C with an undefined upper limit. In other words, which of the following scenarios does the claim language intend to encompass?

   - The temperature for cell growth in step b) is in the range of 31°C to 34°C.
   - The temperature for cell growth in step b) is in the range of 31°C-34°C to an undefined upper limit.

3) Claims 14 and 15 recite the limitation, "and the temperature for growth of infected host cells of step c) is from about 36°C and 38°C." This limitation is not clear because there

is no closure to the "from about" range. The Office has interpreted this phrase to mean that the temperature for growth of infected host cells of step c) is between about 36°C to 38°C. Correction and clarification are required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing adenoviruses using the claimed method, does not reasonably provide enablement for the production of any type of virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims encompasses the production of any type of virus using the sub-optimal temperature protocol described in the claims. The nature of the invention is maximizing virus production under conditions that involve culturing the host cells in sub-optimal

temperatures prior to virus infection. The specification discloses that the invention relates to a method of maximizing production of a thermo-stable virus based on a cell culture temperature shift strategy that results in a substantial enhancement of thermal stable virus production (page 3, lines 19-21). The specification teaches that while any virus which is amenable to production in a temperature controlled cell culture environment is envisioned to fall within the scope of the disclosure, the invention is especially applicable to thermo-stable viruses, such as non-enveloped viruses, including adenoviruses, parvoviruses, reoviruses, and/or picornaviruses (page 7, lines 8-11, and page 3-4, bridging paragraph). Given this teaching, the use of the instant protocols is particularly suited for "thermo-stable" viruses. However, the specification does not clearly define what is meant by "thermo-stable", rather, the specification gives examples of thermo-stable viruses. The term generally encompasses viruses that are not temperature sensitive, but there does not appear to be a defined class of thermo-stable viruses in the art.

The state of the prior art with regard to temperature stress can be found in Shabram *et al.*, (US 5,837,520, "Shabram"). Shabram demonstrates that stressing producer cells can enhance production of viral vectors (col. 39, lines 16-23 and 47-52 of. Producer cells are cells that are engineered to contain a vector genome to be expressed. The stress can be achieved by the introduction of any condition or agent that inhibits cellular growth and/or metabolism, or by altering the level of a pre-existing condition or agent such that it becomes sub-optimal with respect to cellular growth and/or metabolism. Shabram discloses that producer cells of recombinant adeno-associated virus (rAAV) can be stressed with regard to temperature. For example, producer cells can be grown at temperatures above or below the optimum, with optimum temperature being approximately the normal body temperature of the animal from

which the cells are derived. The temperature stress described in Shabram differs from the instant invention which stresses the cells prior to the introduction of the virus; after the introduction of the virus, the temperature of the infected host cells are adjusted back to "at or near a physiologically optimum temperature for producing virus" (instant claim 1).

Nadeau *et al.* (*Biotechnology Advances*, 2003, 20475-489, "Nadeau") offers a review of production of adenovirus vectors for gene therapy. Nadeau discloses that researchers have reported high titers of adenovirus vectors at 35°C as compared to standard infection at 37°C, for perfused cultures (Nadeau, page 484, first full paragraph). Nadeau also notes that others observed that infection at 33°C did not increase yield but resulted in delayed harvest time (Nadeau, page 484, first full paragraph). Cortin *et al.* (*Biotechnol. Prog.* 2004, 20:85-863) discloses that perfusion culture of adenovirus vectors in 293S cells at 35°C improves viral titer by 2.4-fold compared to 37°C (abstract).

The level of one of ordinary skill in the art is high, evidenced by the authors cited in the instant specification and the inventors themselves. The level of predictability in the art of virus production using sub-optimal temperatures prior to virus inoculation is low, given the teachings of the instant specification. The specification discloses that the instant invention is based on a counterintuitive approach involving cell culture/virus production ranges which result in a substantial enhancement of thermal stable virus production. Applicant's working examples demonstrate that production of a recombinant adenovirus serotype 5 encoding a HIV gag transgene shifted down to a sub-optimal level for a period of time prior to the virus infection (then shifted to an optimal temperature post-infection) resulted in a 2-3 fold enhancement (page 7, and Examples). While the results for adenovirus production were unexpectedly higher under

temperature stress conditions, there is no reason for the same to be true of all other viruses. Applicant has not provided a basis on which one can extrapolate the instant findings to other adenoviruses.

Given the breadth of the claims (sub-optimal temperature protocol for any virus), the state of the art, the guidance provided in the specification (sub-optimal temperature protocol for thermostable viruses), the working examples (sub-optimal temperature protocol for adenovirus), the high level of skill and the low level of predictability in the art (Applicant's counterintuitive approach and surprising results), it would require undue experimentation for one of skill in the art to be able to practice the full scope of the claimed methods described in claims 1-4.

Conclusion

No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 1/18/07

STACY B. CHEN
PRIMARY EXAMINER